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(54) Use of certain 5-HT3 receptor antagonists in the treatment of visceral pain

Verwendung von bestimmten 5-HT3-Rezeptorantagonisten zur Behandlung von Eingeweideschmerzen

Emploi de certains antagonistes du récépteur 5-HT3 pour le traitement des douleurs viscérales

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- **NATURE, vol. 316, no. 6024, July 11-17, 1985, pages 126-131; B.P. RICHARDSON et al.: "Identification of serotonin M-receptor subtypes and their specific blockade by a new class of drugs"**
- **THE MERCK MANUAL OF DIAGNOSIS AND THERAPY, 14th Ed., 1982, Merck & Co., Inc., Rahway, N.J., US**
- **Br.J.Pharmacol,100(1990),497-500**
- **Aliment Pharmacol. Ther. 7 (1993) pages 175-180**
- **Ibidem pages 543-551**
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Description

This invention relates to the use of compounds in the preparation of a medicament for the treatment of visceral pain.

'Nature', Vol 316, No 6024, 11-17 July 1985, pages 126-131, WO 85/02847, EP-A-220011, EP-A-189002, EP-A-201165, EP-A-223385, GB 2125398A, EP-A-200444, EP-A-247266, EP-A-235878, EP-A-254584, EP-A-67770, EP-A-158265 and EP-A-158532 disclose classes of compounds which are 5-HT_3 receptor antagonists useful in the treatment of *inter alia* migraine, cluster headache, trigeminal neuralgia and emesis.

It has now been discovered that certain 5-HT_3 receptor antagonists, such as the above classes of compounds, are potentially useful in the treatment of visceral pain.

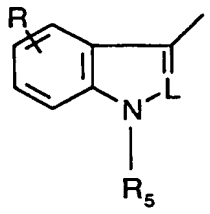
Visceral pain is caused by abnormal distension of hollow visceral organs. In particular, inflation of the colon of patients with irritable bowel syndrome will induce pain in various sites throughout the abdomen, mimicking the disease symptoms (Latimer et al, 1979, J. Behav. Med., 2, 285-295).

Accordingly, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof:

X-CO-Y-Z (I)

wherein

X is a group of formula:



(b)

wherein

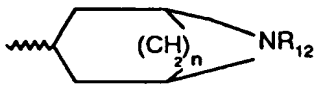
R is hydrogen, halogen or hydroxy;

R_5 is hydrogen or C_{1-6} alkyl; and

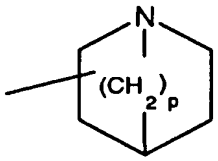
L is CH or N;

Y is NH or O,

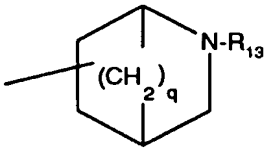
Z is a group of formula (f), (g) or (h):



(f)



(g)



(h)

wherein

n is 2 or 3;

p and q are independently 1 to 3; and

R_{12} or R_{13} is methyl or ethyl; in the manufacture of a medicament for the treatment of visceral pain.

Examples of moieties in alkyl groups in R_5 include methyl, ethyl, *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl, preferably methyl.

R may be 5-, 6- or 7-chloro or fluoro.

R_5 is preferably hydrogen or a methyl or ethyl group.

L is preferably N.

Y is preferably NH.

When Z is a group of sub-formula (f), n is 2 or 3, preferably 3 when L is N.

When Z is a group of sub-formula (g) or (h), p and q are preferably 1 or 2.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, lactic, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, a-keto glutaric, a-glycerophosphoric, and glucose-1-phosphoric acids.

The pharmaceutically acceptable salts of the compounds of the formula (I) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid.

Preferably the acid addition salt is the hydrochloride salt

Pharmaceutically acceptable salts also include quaternary derivatives, examples of which include the compounds quaternised by compounds such as R_{10}-T wherein R_{10} is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_{10} include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl. Suitable examples of Z include halide such as chloride, bromide and iodide.

Pharmaceutically acceptable salts also include internal salts such as pharmaceutically acceptable N-oxides.

The compounds of the formula (I), and their pharmaceutically acceptable salts may also form pharmaceutically acceptable solvates, such as hydrates which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will of course be realised that some of the compounds of the formula (I) have chiral or prochiral centres, and thus are capable of existing in a number of stereoisomeric forms, including enantiomers. The invention extends to each of

these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

Compounds of the formula (I) and their salts may be prepared in accordance with the methods described in the abovementioned UK and European Patent references.

The administration of the compound of formula (I) or a pharmaceutically acceptable salt thereof may be by way of oral or parenteral administration.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.1 to 100mg for example 0.2 to 50mg, of the compound of formula (I) or a pharmaceutically acceptable salt thereof. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0002 to 5 mg/kg/day, more usually 0.0004 to 2.5 mg/kg/day.

No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

It is preferred that the compound of formula (I) or a pharmaceutically acceptable salt thereof is administered in the form of a unit dose pharmaceutical composition in which is combined with a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The following pharmacological data illustrate the invention.

Compound E6 is the Compound of Example 6 of EP-A-200444, N-(endo-9-methyl-9-azabicyclo-[3.3.1]non-3-yl)-1-methyl-indazole-3-carboxamide monohydrochloride (also known as BRL 43694A).

ICS 205-930 is the Compound of Example A-2 of GB 2125398A, indol-3-yl carboxylic acid (endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ester.

Pharmacological Data

Visceral pain in man or in animals is associated with a range of pseudoaffective, pain-related responses which are easily monitored. For example, distension of anaesthetised rat ileum induces a fall in blood pressure which can be blocked by morphine or by capsaicin, indicating that it is part of the pain reflex (Lembeck and Skofitsch, 1982, Naunyn-Schmiedeberg's Arch. Pharmac., 321, 179-183). Furthermore, nociceptive stimuli directed to the intestine can reflexely suppress gastric motility (Abrahamsson et al, 1979, Scand. J. Gastroenterol., 14, 101-106). Compounds which selectively block such pseudoaffective responses may therefore prevent both visceral pain (e.g. pain associated with the irritable bowel syndrome, gall stones, kidney stones, etc) and the paralytic ileus (suppression of gastrointestinal motility) associated with abdominal surgery.

Method

Rats were prepared under urethane anaesthesia for measurement of blood pressure via a cannula in the carotid artery. The whole stomach was intubated with a cannula down the oesophagus and ligated distal to the pyloric sphincter before being filled with 5ml saline. A 3-4cm segment of the duodenum was isolated immediately below the stomach. This segment was connected orally to saline-filled pressure reservoirs with drainage occurring aborally. Distension of the duodenum with a pressure of 75cmH_2O induced a fall in blood pressure and a fall in intragastric pressure, which could be repeated over a series of distensions. Intravenous (i.v.) injection of E6 10mg kg^{-1} reduced both the fall in blood pressure and intragastric pressure caused by duodenal distension

The results are shown in Tables 1 to 3.

TABLE 1

Inhibition by E6 of the fall in blood pressure and intragastric pressure induced by duodenal distension in the anaesthetised rat		
Time (min) after administration of E6 1µg/kg (n=6)	% Inhibition of fall in blood pressure	% Inhibition of fall in intragastric pressure
5	34 ± 16	19 ± 8
10	37 ± 14*	0 ± 13
15	32 ± 14	10 ± 11
20	35 ± 16	9 ± 9
Time (min) after administration of E6 10µg/kg (n=9)	% Inhibition of fall in blood pressure	% Inhibition of fall in intragastric pressure
5	2 ± 17	23 ± 10
10	37 ± 8***	49 ± 15**
15	47 ± 14**	66 ± 15***
20	56 ± 8***	74 ± 14***
Student's 't' test		

*P<0.05;
**P<0.01;
***P<0.005

TABLE 2

Inhibition by ICS 205-930 of the fall in blood pressure and intragastric pressure induced by duodenal distension in the anaesthetised rat		
Time (min) after administration of ICS 205-930 100µg/kg	% Inhibition of fall in blood pressure (n=5)	% Inhibition of fall in intragastric pressure (n=4)
5	8 ± 27	5 ± 13
10	33 ± 7**	37 ± 6**
15	47 ± 18	46 ± 8**
20	45 ± 16*	27 ± 20
Student's 't' test		

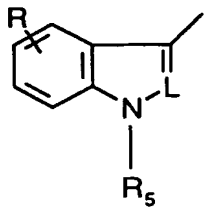
*P<0.05;
**P<0.01

Claims

1. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof:

X-CO-Y-Z (I)

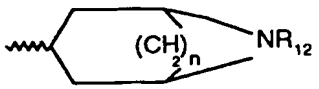
wherein
X is a group of formula:



(b)

wherein
R is hydrogen, halogen or hydroxy;
R_5 is hydrogen or C_{1-6} alkyl; and
L is CH or N;
Y is NH or O,

Z is a group of formula (f), (g) or (h):



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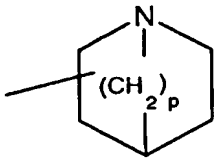

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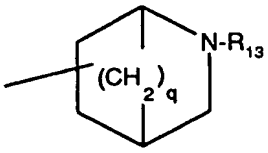


(h)

wherein
n is 2 or 3;
p and q are independently 1 to 3; and
R_{12} or R_{13} is methyl or ethyl; in the manufacture of a medicament for the treatment of visceral pain.

2. A use according to claim 1 wherein R_5 is hydrogen or a methyl or ethyl group.

3. A use according to claim 1 wherein Z is of sub-formula (f) as defined in claim 1, and n is 2 or 3.

4. A use according to claim 1 wherein the compound of formula (I) is N-(*endo*-9-methyl-9- azabicyclo-[3.3.1]non-3-yl)-1-methylindazole-3-carboxamide or a pharmaceutically acceptable salt thereof.

5. A use according to claim 1 wherein the compound of formula (I) is indol-3-yl carboxylic acid (endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ester (ICS 205-930) or a pharmaceutically acceptable salt thereof.

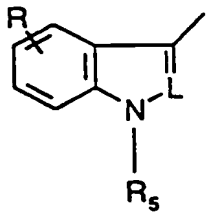
Patentansprüche

1. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon:

X-CO-Y-Z (I)

wobei

X ein Rest der Formel:



(b)

ist, worin

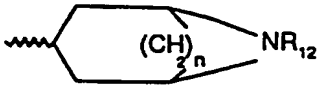
R ein Wasserstoff-, Halogenatom oder eine Hydroxylgruppe ist;

R_5 ein Wasserstoffatom oder ein C_{1-6}-Alkylrest ist; und

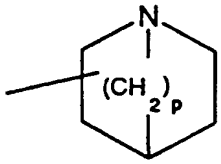
L eine CH-Gruppe oder ein N-Atom ist;

Y eine NH-Gruppe oder ein O-Atom ist;

Z ein Rest der Formel (f), (g) oder (h)



(f)



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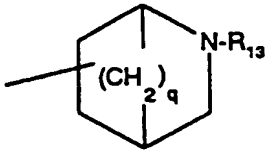


(h)

ist, worin

n 2 oder 3 ist;

p und q unabhängig 1 bis 3 sind; und

R_{12} oder R_{13} eine Methyl- oder Ethylgruppe ist;

zur Herstellung eines Medikamentes zur Behandlung von Viszeralschmerz.

2. Verwendung nach Anspruch 1, wobei R_5 ein Wasserstoffatom oder eine Methyl- oder Ethylgruppe ist.

3. Verwendung nach Anspruch 1, wobei Z die in Anspruch 1 definierte Formel (f) ist, und n 2 oder 3 ist.

4. Verwendung nach Anspruch 1, wobei die Verbindung der Formel (I) N-(endo-9-Methyl-9-azabicyclo-[3.3.1]non-3-yl)-1-methylindazol-3-carboxamid oder ein pharmazeutisch verträgliches Salz davon ist.

5. Verwendung nach Anspruch 1, wobei die Verbindung der Formel (I) Indol-3-carbonsäure(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ester (ICS 205-930) oder ein pharmazeutisch verträgliches Salz davon ist.

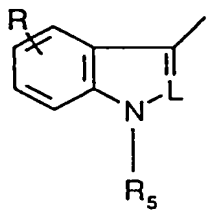
Revendications

1. Utilisation d'un composé de formule (I), ou d'un de ses sels pharmaceutiquement acceptables :

X-CO-Y-Z (I)

formule dans laquelle

X représente un groupe de formule :

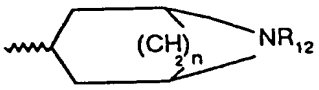


(b)

dans laquelle

R représente l'hydrogène, un halogène ou un groupe hydroxy ;
R_5 représente l'hydrogène ou un groupe alkyle en C_1 à C_6, et
L représente un groupe CH ou N ;
Y représente un groupe NH ou O ;

Z représente un groupe de formule (f), (g) ou (h) ;



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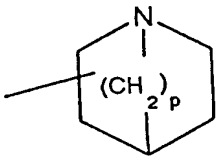

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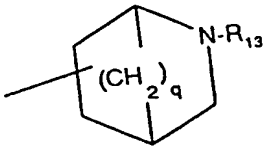

(h)

dans laquelle

n	est égal à 2 ou 3 ;
p et q	ont indépendamment une valeur de 1 à 3 ; et
R_{12} ou R_{13}	représente un groupe méthyle ou éthyle ; dans la production d'un médicament pour le traitement de la douleur viscérale.

2. Utilisation suivant la revendication 1, dans laquelle R_5 représente l'hydrogène ou un groupe méthyle ou éthyle.

3. Utilisation suivant la revendication 1, dans laquelle Z répond à la sous-formule (f) telle qu'elle est définie dans la revendication 1, et n est égal à 2 ou 3.

4. Utilisation suivant la revendication 1, dans laquelle le composé de formule (I) consiste en le N-(endo-9-méthyl-9-azabicyclo-[3.3.1]non-3-yl)-1-méthyl-indazole-3-carboxamide ou un de ses sels pharmaceutiquement acceptables.

5. Utilisation suivant la revendication 1, dans laquelle le composé de formule (I) consiste en l'ester (endo-8-méthyl-8-azabicyclo[3.3.1]oct-3-ylique) d'acide indol-3-yle-carboxylique (ICS 205-930) ou un de ses sels pharmaceutiquement acceptables.